

CLAIMS:

1. A process for producing a cross-linked polysaccharide gel comprising:
  - (a) contacting a polysaccharide mixed in an alkaline medium with a bifunctional or polyfunctional epoxide to provide an essentially epoxy cross-linked polysaccharide
  - 5 wherein the epoxide is substantially linked to the polysaccharide by ether bonds;
  - (b) drying the epoxy cross-linked polysaccharide without substantially removing epoxide from the alkaline medium to form a cross-linked polysaccharide matrix;
  - (c) optionally washing the cross-linked polysaccharide matrix with a water miscible solvent; and
  - 10 (d) neutralising the cross-linked polysaccharide matrix with an acidic medium to form a cross-linked polysaccharide gel.
2. The process according to claim 1 wherein the polysaccharide is hyaluronic acid, pectin, xanthan or alginic acid.
3. The process according to claim 1 or 2 wherein the polysaccharide is an anionic
- 15 derivative of carboxymethyl cellulose, carboxymethyl dextran, hyaluronic acid or carboxymethyl starch.
4. The process according to claim 3 wherein the polysaccharide is hyaluronic acid.
5. The process according to any one of claims 1 to 4 wherein the epoxide is 1,4 – butanediol diglycidyl ether, 1,2-ethanediol diglycidyl ether or an epoxy-substituted
- 20 pentaerythritol.
6. The process according to claim 5 wherein the epoxide is 1,4 –butanediol diglycidyl ether.
7. The process according to any one of claims 1 to 6 wherein the alkaline medium has a pH in the range of about 9 to 12.
- 25 8. The process according to any one of claims 1 to 7 wherein the alkaline medium comprises between 1 and 5 wt/vol percent polysaccharide and between 0.05 and 0.5 wt/vol percent epoxide.
9. The process according to any one of claims 1 to 8 wherein the epoxide contacts the polysaccharide at a temperature of at least about 45°C.
- 30 10. The process according to any one of claims 1 to 9 wherein the polysaccharide matrix is dried under vacuum at a temperature of at least about 35°C.
11. The process according to any one of claims 1 to 10 wherein steps (a) to (c) are performed under alkaline conditions.

12. The process according to any one of claims 1 to 11 wherein the optional washing step (c) further comprises washing the cross-linked polysaccharide matrix with acetone.
13. The process according to any one of claims 1 to 12 wherein the neutralisation step (d) further comprises freeze drying the cross-linked polysaccharide gel and  
5 reconstituting the gel.
14. The process according to claim 13 wherein the freeze dried cross-linked polysaccharide gel is reconstituted in phosphate buffered saline.
15. The process according to any one of claims 1 to 14 further comprising combining the polysaccharide with a biologically active substance.
- 10 16. A cross-linked polysaccharide gel substantially resistant to hyaluronidase degradation prepared by the process according to any one of claims 1 to 15.
17. A biocompatible gel comprising hyaluronic acid cross-linked substantially by ether bonds with 1,4-butanediol diglycidyl ether such that the gel is sufficiently cross-linked to substantially resist degradation.
- 15 18. The gel according to claim 17 wherein the gel releases less than about 75 percent uronic acid under hyaluronidase treatment.
19. The gel according to claim 17 wherein the gel releases no more than about 70 percent uronic acid under hyaluronidase treatment.
20. The gel according to claim 17 wherein the gel releases no more than about 65  
20 percent uronic acid under hyaluronidase treatment.
21. The gel of claim 17 wherein the gel releases less than about 75 percent uronic acid after being extruded or expelled from a 32 gauge needle.
22. The gel according to claim 17 wherein the gel releases no more than about 70 percent uronic acid after being extruded or expelled from a 30 gauge needle.
- 25 23. The gel according to any one of claims 17 to 22 further comprising a biologically active substance.
24. The gel according to claim 23 wherein the biologically active substance is a hormone, cytokine, vaccine, cell, tissue augmenting substance, or mixture thereof.
25. The gel according to claim 24 wherein the tissue augmenting substance is  
30 collagen, starch, dextranomer, polylactide, poly-beta-hydroxybutyrate, or copolymers thereof.

26. The gel according to claim 23 wherein the biologically active substance is an alkaloid, peptide, phenothiazine, benzodiazepine, thioxanthene, hormone, vitamin, anticonvulsant, antipsychotic, antiemetic, anesthetic, hypnotic, anorexigenic, tranquilizer, muscle relaxant, coronary vasodilator, antineoplastic, antibiotic, antibacterial, antiviral,  
5 antimalarial, carbonic anhydrase inhibitor, nonsteroid antiinflammatory agent, vasoconstrictor, cholinergic agonist, cholinergic antagonist, adrenergic agonist, adrenergic antagonist narcotic antagonist or combination thereof.

27. A pharmaceutical composition comprising:

a cross-linked polysaccharide gel according to claim 16;

10 a biologically active substance; and

a pharmaceutically acceptable carrier.

28. A pharmaceutical composition comprising:

a biocompatible gel according to any one of claims 17 to 22;

a biologically active substance; and

15 a pharmaceutically acceptable carrier.

29. The pharmaceutical composition according to claim 27 or 28 wherein the preparation is in the form of a pill, tablet, capsule, suppository, spray, cream ointment or sticking plaster.

30. A method of treating or preventing a disorder in a subject in need thereof,  
20 comprising administering a therapeutically effective amount of a gel according to any one or more of claims 16 to 26.

31. A method of treating or preventing a disorder in a subject in need thereof, comprising administering a therapeutically effective amount of a pharmaceutical composition according to any one of claims 27 to 29.

25 32. The method according to claim 30 or 31, wherein the administration to the subject is by injection.

33. The method according to claim 30 or 31, wherein the administration to the subject is by topical application.

34. Use of a gel according to any one or more of claims 16 to 26 for the manufacture  
30 of a medicament for treating or preventing a disorder in a subject in need thereof.

32. Use of a pharmaceutical composition according to any one of claims 27 to 29 for the manufacture of a medicament for treating or preventing a disorder in a subject in need thereof.